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Because both noninvasive pharmacotherapeutic options, as well as myriad surgical approaches, are available for managing patients with ectopic pregnancy (EP), emergency physicians are faced with the challenge of risk-stratifying patients into subgroups that are eligible for a specific therapeutic program. More than anything, this means confirming the diagnosis of EP as early as possible in the natural history of the condition, thereby permitting consideration of a wider range of management approaches.

These clinical obstacles to making a precise diagnosis are well known, and consequently, a systemic approach to patient evaluation is recommended. During the first 20 weeks of gestation, the differential diagnosis of EP includes spontaneous miscarriage and other trophoblastic disorders. Fortunately, with the availability of serum hormone analysis, transvaginal ultrasonography, and more invasive strategies, the diagnosis of EP can be confirmed early in pregnancy, thereby permitting a greater percentage of patients to be treated with noninvasive, medical approaches such as methotrexate.

Spontaneous miscarriage also requires a systematic approach to diagnosis in order to identify patients who can be treated expectantly vs. those who require dilatation and curettage.

Trophoblastic disorders, although not common, may also confuse the diagnosis, and must be excluded in the majority of cases.

Part I of this three-part series discussed, in detail, the diagnostic strategies available for EP. Part II, the current issue, presents an algorithmic approach to the differential diagnosis of vaginal bleeding during the first 20 weeks of pregnancy. Finally, risk-stratification strategies are discussed in detail that permit the physician to select the least invasive treatment strategy for individual patients with EP and other disorders during early pregnancy.

— The Editor

Vaginal Bleeding During the First 20 Weeks of Pregnancy: Guidelines for ED Evaluation and Management

Part II: Differential Diagnosis and Management of Ectopic Pregnancy and Spontaneous Miscarriage

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Differential Diagnosis of Ectopic Pregnancy: Improving Accuracy of Detection

The incidence of EP increased nearly five-fold between 1980 and 1992, a period during which the diagnosis of this condition also became more accurate.[1] In the 1970s, for example, establishing an accurate diagnosis of pregnancy in these patients was a significant problem; in fact, the false-negative rate for pregnancy tests in patients with EP was reported to be as high as 50%.[2] Fortunately, the diagnostic challenge in patients with EP

has been minimized by the availability of increasing sensitive laboratory tests.

Presently, the pregnancy tests most commonly used in the emergency department (ED) are based on the enzyme-linked immunosorbent assay (ELISA), and are highly sensitive and specific. Beta-hCG urine concentrations of approximately 20 mIU/mL and 10 mIU/mL in serum can be detected in the most sensitive ELISA tests. False negatives are reported to be as low as 1% for urine testing and 0.5% for serum testing. False negatives may occur in the presence of renal failure and dilute urine and very early in pregnancy.[3,4] Current transvaginal ultrasonographic technology can identify intrauterine pregnancies at around 35 days gestation or beginning during the first week after a missed period.

Preventing Misdiagnosis. Despite quantifiable improvements in diagnostic technology, the misdiagnosis of EP is not an infrequent occurrence. In one older review of 86 fatal ectopic pregnancies, almost 50% of these patients had seen a physician and were given an alternate diagnosis prior to their death.[5]

A more recent review published in 1990 still reported that up to 40% of patients later confirmed as having an EP were misdiagnosed on their first ED visit.[6] The authors examined 28 patients with misdiagnosis and compared them to 37 patients in whom the diagnosis was successfully made during their first visit to the ED. They found that misdiagnosed patients had fewer complaints of severe pain and had less tenderness on exam than the control group. A significant percentage of misdiagnosed patients had no complaints of pain whatsoever on their first visits. About 56% of ultrasonographic exams in the missed patients were considered nondiagnostic, but these were transabdominal studies. Nine of the 28 patients had culdocentesis on the first visit, and all of the taps were nondiagnostic. The beta-hCG levels in patients with missed ED varied widely, ranging from 100 mIU/mL to greater than 10,000 mIU/mL.

The time required to make an accurate diagnosis of EP in patients who were initially misdiagnosed varied from 24 hours to 15 days. Several conclusions and recommendations aimed at preventing misdiagnosis of EP were presented. First, the most common misdiagnosis was spontaneous miscarriage. Many of these patients presented with crampy abdominal pain during the initial presentation, and in some cases, the pain decreased with time. In several cases, the passage of tissue was interpreted as a sign of miscarriage, although this diagnosis was not subsequently confirmed by examination of the tissue for villi. (Note: In EP, endometrial tissue may slough off and give the appearance of products of conception but no chorionic villi will be found under close examination.)

Of special concern was the finding that almost 32% of patients in whom the diagnosis was originally missed had signs of hypovolemia during their first visit, a finding that was attributed to causes other than blood loss. Some patients had orthostatic changes of greater than 30 mmHg in blood pressure, and others had a 14% decrease in their hematocrit. These changes were inappropriately explained as being a result of dehydration or hemodilution from saline administration, or they were simply overlooked. Finally, all of the women in whom EP was missed had a history of at least one risk factor for EP.

Differential Diagnosis. The differential diagnosis of EP is summarized in Table 1. Among the list of diseases that may be confused with EP, threatened or incomplete miscarriage is the most common misdiagnosis. These patients can present in a very similar fashion; they may have have falling beta-hCG levels, and occasionally, ultrasonographic findings may be similar. From a diagnostic perspective, an os that is open to a fingertip is indicative of a spontaneous miscarriage, and can be a useful physical finding. When the clinician is in doubt of the diagnosis, the patient should undergo uterine curettage to examine for chorionic villi. If none are seen, the patient is at very high risk for EP and should proceed to diagnostic laparoscopy. Finally, heterotopic pregnancy is much more common in patients using assisted reproduction techniques. Consequently, identification of an intrauterine pregnancy or confirmation of miscarriage

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Table 1. Differential Diagnosis of Ectopic Pregnancy

• Normal intrauterine pregnancy	Threatened or incomplete miscarriage
• Ovarian cysts (rupture, unruptured)	Appendicitis
• Acute salpingitis	Tubo-ovarian abscess
• Gastroenteritis	Torsion of ovary or fibroid
• Diverticulitis	Renal calculi
• Pyelonephritis	Endometriosis

Adapted from: Mallett VT. Ectopic pregnancy. In: Pearlman MD, Tintinalli JE, eds. *Emergency Care of the Woman.* New York: McGraw Hill; 1998:21-28; and Lewis FR, Holcroft JW, Boey J, et al. Appendicitis: A critical review of diagnosis and treatment in 1,000 cases. *Arch Surg* 1975;110:677-684.

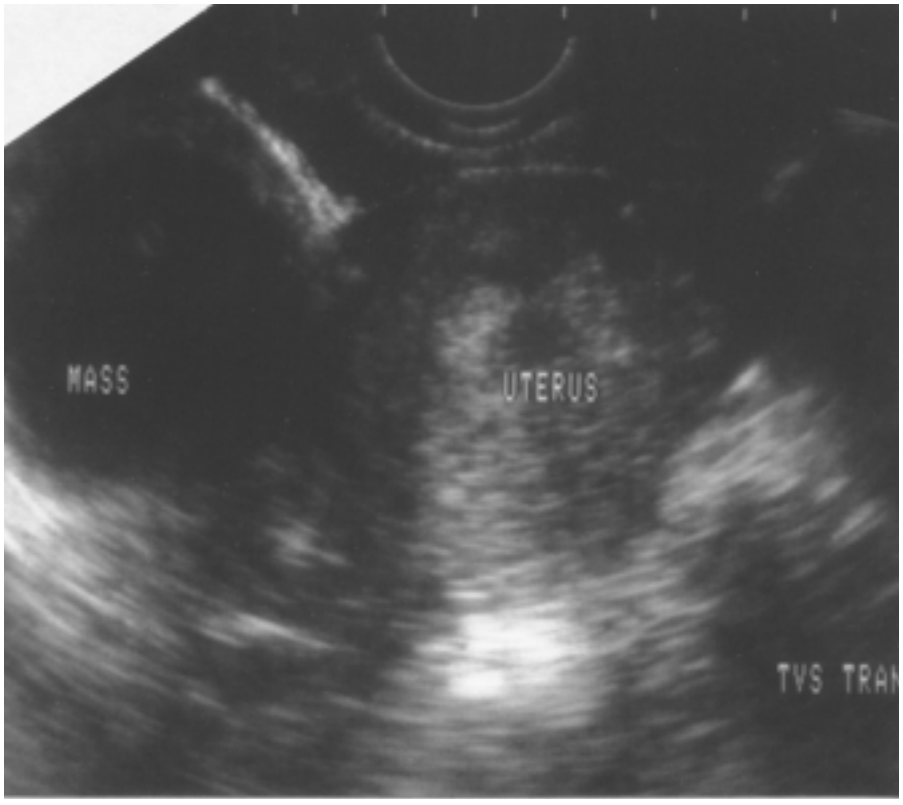
may not be enough to rule out ectopic in this subgroup of patients.

Ovarian cysts are common in early pregnancy, and they also have a propensity to rupture. When a ruptured cyst produces hemoperitoneum, this condition may be difficult to distinguish from the rupture of an EP.[7] Although a culdocentesis can be helpful in some cases, clinical evidence of hemoperitoneum in these patients will usually require surgical intervention to confirm the correct diagnosis and establish an appropriate treatment plan.

Patients with pelvic inflammatory disease (PID) also may be confused with women suspected of having an EP. Although PID is rare in pregnancy because presence of the cervical mucus plug should prevent ascending infection, in rare cases PID may still be seen in the earlier stages. One possible explanation is that the infection was present prior to the pregnancy. In addition, patients with EP can present with fever, further confusing the picture. However, presence of a positive pregnancy test obligates the physician to rule out EP first, even if the working diagnosis is PID or tubo-ovarian abscess. A transvaginal ultrasound study can sometimes confirm a diagnosis, but in some patients only a laparoscopic examination will be confirmatory. *(See Figures 1-3.)*

Appendicitis is easily misdiagnosed in women of childbearing age, with reported negative laparotomy rates approaching 50% in pregnant patients.[8] Pregnant women can be even more confusing. Right lower quadrant pain/tenderness, elevated white blood cell counts, and fever are overlapping findings in both diseases. In some cases, a laparoscopic study is required for final diagnosis. Complications of endometriosis, ovarian torsion, or torsion of a uterine fibroid can also be confused with EP, but in these patients ultrasound studies can often identify the problem. In summary, when faced with a pregnant patient, laparoscopy may be required to differentiate between EP and other diagnoses with similar presentations.

Figure 1. Ultrasound Image of Ectopic Pregnancy



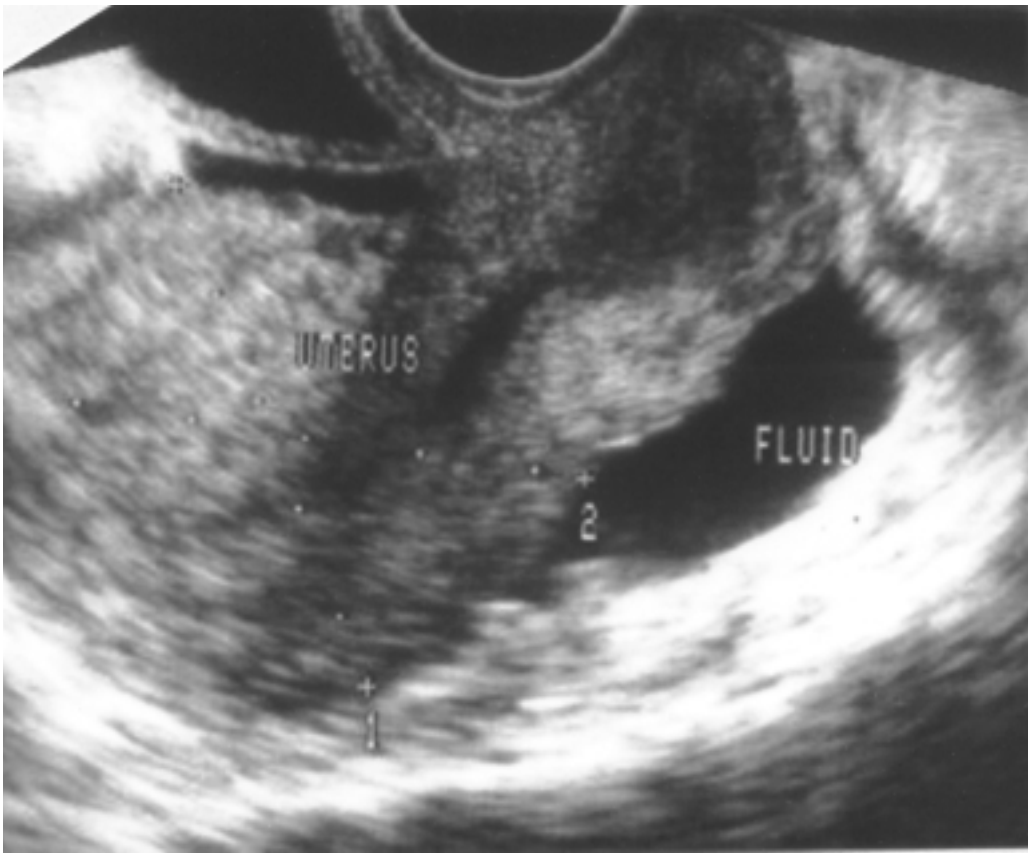
In Figure 1, a large hyperechogenic mass is noted adjacent to the uterus, representing an ectopic pregnancy.

Diagnostic Algorithms. A number of diagnostic algorithms have been proposed to assist in rapid and efficient identification of patients with EP. The objective of these algorithms is to reduce the rate of misdiagnosis. Many diagnostic algorithms for stable patients have been developed, an example of which is presented in Figure 4.[9-11]

Up to 20% of patients with EP will have signs of hemodynamic instability or significant peritonitis; clearly, these patients should be resuscitated with ABCs in mind and they should have urgent surgical consultation. For the remaining 80% of patients, algorithms can be useful. Proposed algorithms of EP detection vary, but in general, they rely on a combination of serum markers and transvaginal ultrasound.

Without exception, a single (or serial) beta-hCGs or progesterone level is required as part of the systematic evaluation of all patients suspected of having EP. These levels are interpreted in conjunction with transvaginal ultrasonographic studies. If there is ultrasonographic evidence of EP, the patient should receive either medical or surgical treatment for EP. However, if the beta-hCG is above the discriminatory threshold (around 1500 mIU/mL) and the ultrasound is indeterminate or shows no intrauterine pregnancy, the patient is still

Figure 2. Ultrasound Image of Free Fluid in Cul-de-sac



In Figure 2, the ectopic pregnancy is not seen, but evidence of rupture is seen as free fluid in the cul-de-sac.

considered to be high risk for an EP, and appropriate consultation is required.

One large series found a 25% incidence of EP in patients with beta-hCG greater than 1500 mIU/mL and nondiagnostic ultrasound.[12] If the beta-hCG is less than the discriminatory threshold, the patient may still have EP, but the diagnosis will typically be unclear until serial beta-hCG levels can be taken. It may be possible to follow these patients in the outpatient setting, with the consultant monitoring the serial enzyme levels and repeating ultrasound studies to confirm the diagnosis. All discharged patients should be given appropriate instructions for EP and threatened miscarriage.

Outpatient follow-up consists of repeat beta-hCG in 48 hours and ultrasound if the level rises above the discriminatory threshold. Ultrasound has been shown in a large series to be diagnostic in 80% of patients with beta-hCG above 1500 mIU/mL.[13] Although using serial beta-hCG levels has been shown to be 97% sensitive and 95% specific, a potential disadvantage of this approach is delay of diagnosis.[14]

Algorithms that rely on a single progesterone level have been shown to be 100% accurate in one series, and have the advantage of not requiring serial levels.[10] If the ultrasound is not diagnostic, and the progesterone is higher than 25 ng/mL, the pregnancy is likely to be normal. Uterine curettage for diagnosis is performed in cases where the progesterone level is less than 5 ng/mL, or when serial beta-hCG levels plateau or fall. It should be stressed that even when beta-hCG levels never rise above the discriminatory threshold, the patient is still at considerable risk of EP. Uterine curettage is again recommended to distinguish between failed intrauterine pregnancy and EP.

Several precautions are advised when managing patients in the outpatient setting. First, the ED physician should note that the rupture has been reported in individuals with very low beta-hCG levels—in some cases in patients with a level as low as less than 10 mIU/mL.[15] The patient should not be discharged to stay at home alone. If sudden hypotension develops, she may not be able to call for help. Finally, any patient who is being evaluated for possible EP and is to be discharged should not be sent out without a phone call to the OB/GYN consultant who will be performing the follow-up visit.

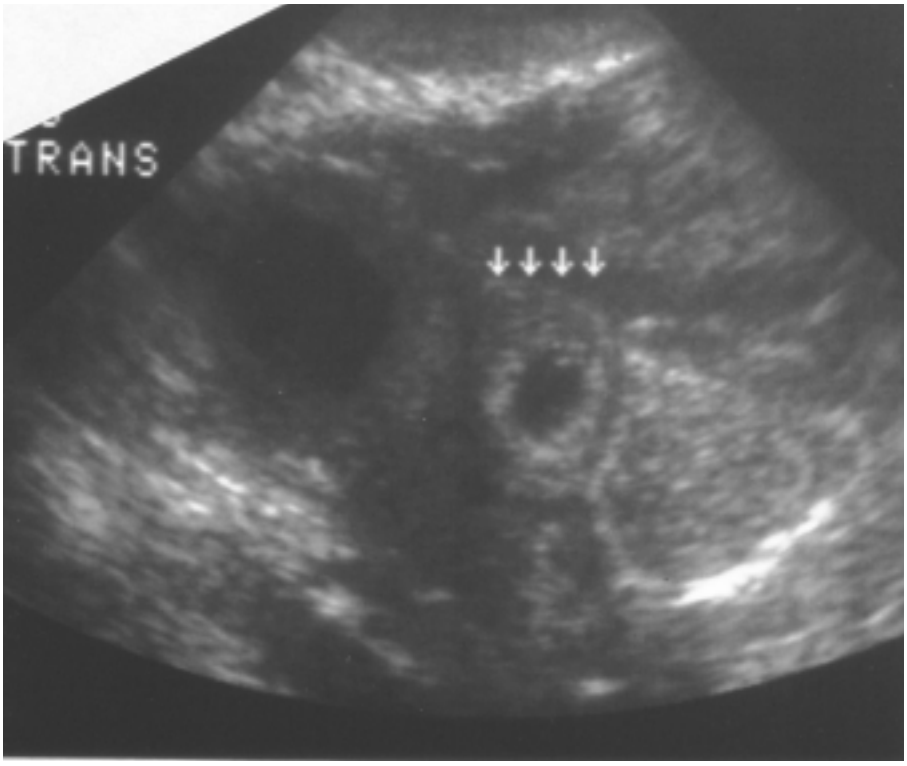
Ensuring appropriate and timely follow-up for these patients is essential. Making their obstetrician aware of the situation gives them the chance to call the patient and remind them to follow-up if the patient does not choose to do so on her own. Patients in whom follow-up cannot be reasonably assured, for whatever reason, should be referred for inpatient evaluation or observation.

Management of Ectopic Pregnancy

Overview. Fortunately, the care of patients with suspected EP has greatly improved over the years. The first successful surgery for EP was performed in 1883, and until recently, surgical intervention was the mainstay of treatment.[16] In decades past, the diagnosis of EP usually was not made until the operation was performed, and one needed high suspicion of the diagnosis to commit to laparotomy. As a result, most patients were not treated until symptoms of rupture had become clear, making early intervention all but impossible.

The introduction of laparoscopic surgical techniques further improved management of patients with EP. The performance of a salpingotomy (removal of the involved section of the fallopian tube) or linear salpingostomy (removal of products of conception via an incision in the tube) also marked improvements in management by increasing the chance for future fertility in these patients. However, the most dramatic change in therapy was the introduction in 1982 of medical treatment, the mainstay

Figure 3. Ultrasound Image of Tubal Ring



In Figure 3, a tubal ring or "ring of fire" sign is seen. A small, hypoechogenic mass is seen surrounded by a hyperechogenic area representing an ectopic gestational sac and surrounding decidual reaction.

of which is methotrexate, in a select subset of eligible patients.[17]

When indicated and appropriate, methotrexate is now commonly used for medical management of EP and has shown success rates equivalent to those of surgical intervention.[17] As a result, early diagnosis of EP is now more important than ever because it permits consideration of different treatment options, decreases morbidity and mortality, and may help reduce the incidence of future ectopic pregnancies. The following section will review and summarize currently recommended medical and surgical management strategies in patients with confirmed EP.

Medical Management. In many medical centers, medical management of EP is now considered to be the treatment of choice for EP. The reasons for this include lack of surgical complications and lower cost of treatment.

In the United States in 1990, it was estimated that the total cost of care for EP was $1.1 billion. In one study conducted at a university-based teaching hospital, average total cost was $1563 for medical treatment, $6626 for laparoscopic treatment, and $8001 for laparotomy.[18]

Mean length of hospital stay also varied-2.5 days for laparoscopic care vs. 5.2 days for laparotomy.[18]

After the initial report of successful medical management in 1982, many clinical trials followed and all found that outcome with medical treatment for unruptured EP was similar to that for laparoscopic salpingostomy.[18] So far, however, only one randomized comparison comparing the two treatments has been performed. In 1997, one group presented data demonstrating that in patients without signs of rupture, methotrexate was as effective as laparoscopic salpingostomy.[17] Furthermore, they found that subsequent rates of successful pregnancies were also the same in both treatment groups.[20] Methotrexate has also been used successfully to treat more unusual ectopic locations, such as cornual pregnancies, that previously were only managed with surgery.

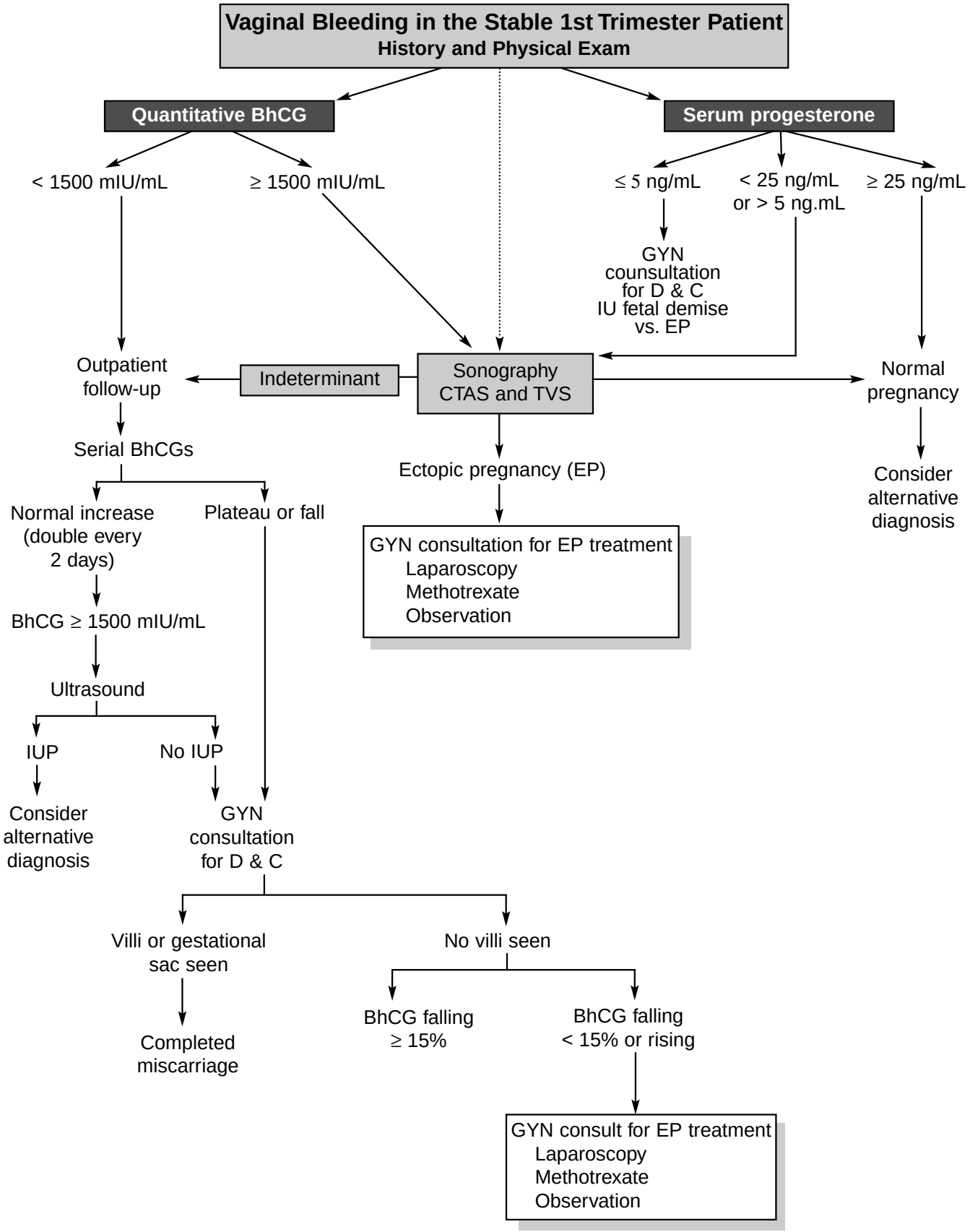
To maximize the usefulness, safety, and efficacy of medical management, certain inclusionary and exclusionary patient criteria must be met. In particular, contraindications are designed to avoid treating more advanced cases in which the risk of rupture is significant. Contraindications to medical treatment of EP include: obvious signs of rupture (hemoperitoneum, severe pain), diameter of adnexal mass (> 3-4 cm on ultrasound), beta-hCG greater than 2000 mIU/mL, evidence of cardiac activity, and/or suspected heterotopic pregnancy.[21] Accordingly, early diagnosis of EP is essential for optimizing patient outcomes and enabling the consultant to use this approach.

Methotrexate is currently the drug of choice for medical management of EP. This agent inhibits synthesis of purines and pyrimidines and, therefore, prevents DNA synthesis and cell division. Clearly, methotrexate is not specific for ectopic tissue, and its side effects include bone marrow suppression, hepatotoxicity, stomatitis, pulmonary fibrosis, and photosensitivity.[21] Side effects can be treated and minimized with leucorvorin.[22]

Two methotrexate regimens currently are used: single dose and "variable" dose treatment. Single dose is used more often and, although it is more convenient, it is slightly less successful than the variable dose method. Single-dose methotrexate therapy has been reported to have an overall success rate of 82%, with 4% of the total treated group requiring a second dose for rising beta-hCG levels and 14% eventually requiring surgical intervention for bleeding or rupture.[19] In contrast, variable dose regimens were successful in 93% of patients; both regimens have similar rates of success for subsequent pregnancy (58% variable, 61% single dose).[23]

Methotrexate treatment may administered as inpatient treatment, but single-dose therapy given intramuscularly can also be performed in the outpatient setting, thereby avoiding hospitalization. If a patient is being discharged from the ED with an injection of methotrexate, the importance of follow-up with their OB to obtain serial beta-hCG levels must be stressed, as well as educating the patient about warning signs of rupture. Lastly, one is reminded to always check the Rh status in these

Figure 4. Algorithm for ED Evaluation of Vaginal Bleeding or Pain in the First Twenty Weeks of Pregnancy



Adapted from Pisa MD, Carson SA. Ectopic pregnancy. In: Scott JR, et al, eds. *Danforth's Obstetrics and Gynecology*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:155-172; and Abbott JT. Acute complications related to pregnancy. In: Rosen P, et al, eds. *Emergency Medicine: Concepts and Clinical Practice*. 4th edition. Mosby-Year Book, Inc; 1998:2342-2364.

patients, and treat Rh-negative mothers with Rhogam. *(See section on Rhesus Factor.)*

Surgical Treatment. When the first successful surgical treatment of EP was performed in 1883, four patients survived the procedure—an amazing outcome at the time.[16] In 1973, the first laparoscopic surgery was performed, and it soon became the surgical treatment of choice for EP.[24] As with medical management, early diagnosis of EP is essential to avoid open laparotomy.

The laparoscopic approach has been shown superior to laparotomy in three different prospective randomized trials.[25] In this regard, use of the laparoscope leads to lower cost, shorter hospital stays, less blood loss, less analgesia, shorter operating room times, and more rapid return to work. The ability to carry a successful subsequent pregnancy is similar with either method. The laparoscope has been used with good results in treatment of less common ectopic locations as well, including ovarian, interstitial, and early abdominal pregnancies. For traditional tubal pregnancies, linear salpingostomy (removal of products of conception via an incision in the tube) instead of traditional salpingectomy (removal of the entire tube) produced better future fertility rates, but has a higher risk of recurrent EP.

Persistent EP is one of the main complications of surgery, and occurs in 8% of linear salpingostomy patients vs. 4% of laparotomy patients.[25] This complication results from the presence of retained trophoblastic tissue, and is diagnosed by following beta-hCG levels after surgery. If the beta-hCG level has not fallen to less than 50% of the preoperative value on the first postoperative day, there is an 85% chance of persistent EP.[26] Persistent EP can be treated successfully by single-dose methotrexate.

New Treatment Advances. Two new treatment approaches have recently been developed for EP. The first is direct injection of ectopic tissue with methotrexate using ultrasonographic guidance. This approach was first described in 1987, and to date 12 studies totaling 406 patients have been published.[25] Substances other than methotrexate have also been used (i.e., hyperosmolar glucose) in attempts to avoid the potential toxicity of methotrexate.[27] In fact, this approach is associated with fewer side effects, yet produces higher local concentrations of methotrexate.

The direct injection technique can be used in patients with baseline hepatic or renal abnormalities, in whom systemic methotrexate may be contraindicated. The biggest disadvantage is that the technique requires an experienced operator to reduce risk of infection, bleeding, and tubal damage at the injection site. At present, direct injection is only being performed at a few centers and lacks general acceptance. Success rates are similar to single-dose systemic methotrexate, with an 81% overall success rate among the 406 patients included.[28] A 47% rate of successful subsequent pregnancy was reported.[28]

Ironically, the second "new approach" replicates a strategy that was used before surgical intervention was developed (i.e., "expectant management"). Before the advent of surgery, EP was not a uniformly fatal disease, with some patients having spontaneous regression or tubal abortion without deleterious effects. The "watchful waiting" approach was again attempted in an effort to preserve fertility when salpingectomy was the only surgical option, and it is currently begin explored again in an effort to reduce risks and costs of treatment.

The first study reporting on the outcomes of expectant management was in 1955, and the results were problematic.[29] Only 57% of patients resolved, 20% needed surgery for persistent symptoms, and another 23% needed surgery for catastrophic bleeding.[102] Given these results, it is not surprising that no additional attempts using this technique were reported again until 1982. In fact, strict selection criteria for patients has led to a total of 363 patients being reported in 12 studies world-wide since 1982.[30]

Current studies select for patients at very low risk for rupture. The range of beta-hCG levels in these studies is between 250 mIU/mL up to 2,500 mIU/mL.[31,32] Other studies simply select patients with falling beta-hCG levels or the following: a tubal mass of less than 2-3 cm diagnosed by laparoscope, empty uterus on ultrasound, and lack of fetal cardiac motion.[30] Interestingly, when these inclusionary and exclusionary criteria are used, studies have reported an overall success rate of 67%, with rupture in only 2.5% of patients.[30]

It is important to note that some of the ruptures have occurred in patients with very low beta-hCG levels (i.e., between 41 mIU/mL and 212 mIU/mL).[30] Subsequent successful pregnancy rates of 68% were reported for the 363 patients.[30] Overall, the authors suggest that up to 15-20% of patients with a diagnosis of EP may be appropriate candidates for expectant management. They suggest the following criteria to identify eligible patients: minimal pain, minimal vaginal bleeding, no rupture (free fluid), falling beta-hCG levels with initial levels less than 1,000 mIU/mL, no ectopic cardiac motion, and ectopic mass less than 3 cm.[30] Current American College of Obstetrics and Gynecology (ACOG) recommendations suggest this approach can be used in patients with a decreasing beta-hCG less than 200 mIU/mL. Patients must understand the associated risk of rupture, bleeding, and that a need for further treatment may be required.[33]

Spontaneous Miscarriage

Spontaneous miscarriage is a common diagnosis in patients with vaginal bleeding that occurs during the first half of pregnancy. It is estimated that 15% of clinically proven pregnancies end in miscarriage, with the majority occurring before 12 weeks gestation.[34] Moreover, because some patients may miscarry before they are known to be pregnant, the actual miscarriage rate may be as much as 2-3 times higher than reported.

Up to 20% of pregnant women will experience vaginal bleeding during the first weeks of pregnancy, and as many as 50% of them will progress to miscarriage.[35] The risk of miscarriage varies greatly with age. For patients younger than 20 years, the risk averages only 12%, whereas in patients older than 45 years it approaches 50%.[36] As the term "abortion" has a negative connotation to many patients, it is gradually being replaced in the literature with "miscarriage." This section will review causes and risk factors for spontaneous miscarriage, and discuss in

detail the ED evaluation and management of various presentations of miscarriage.

When evaluating pregnant patients with vaginal bleeding, ED physicians must recognize that maternal trauma from domestic abuse is common and, at times, may be occult in its presentation. Hence, all pregnant women should routinely be screened for abuse. A history of substance abuse, depression, or multiple ED visits should alert the physician to the possibility of abuse. The abuser is usually confrontational toward the staff and overprotective of the patient. Abuse is more likely to be identified if the patient is questioned in a private setting and in a non-judgmental and direct manner.[37] Emotional status and safety must be addressed before the patient is discharged from the ED.[38]

Pathophysiology. Spontaneous miscarriage may result from abnormal embryo development or from maternal factors. Up to 50% of women with spotting or cramping early in pregnancy will have an abnormal intrauterine pregnancy on initial ultrasound, with many of these embryos being morphologically abnormal.[39] Approximately 33% of miscarried specimens lost before 9 weeks are due to anembryonic development, termed a "blighted ovum."[40] In this case, only an empty gestational sac is seen on ultrasound.

The significant percentage of embryonic abnormalities represents a natural process that eliminates almost 95% of cytogenetic defects before birth. The rate of identified chromosome defects in miscarried embryos from the first trimester approaches 60%, and falls to 7% by the end of the 24th week.[34] In most cases, the parents have normal karyotypes, and the abnormal conceptus is the result of a random genetic error. However, a small number of parents may carry balanced translocations and they will give rise to recurrent miscarriages. Patients with recurrent miscarriage require obstetric evaluation to identify the cause when possible, as some will be due to treatable conditions such as cervical incompetence.

Much attention in the lay press has been given to chemical and infectious agents as a potential cause of spontaneous miscarriage, including tobacco use, coffee, alcohol, illicit drugs, Salmonella, shingles, Mycoplasma, and various sexually transmitted diseases. While many of these agents can increase the risk of miscarriage, it is felt that such extrinsic factors account for a small percentage of spontaneous miscarriage.[41] An important point is that birth control pills, video display terminals, minor abdominal trauma in the first trimester, and diagnostic x-rays less than 10 rads have been shown *not* to increase pregnancy loss.[42]

ED Evaluation and Management. Patients who present to the ED early in pregnancy with abdominal pain and/or vaginal bleeding are at risk for spontaneous miscarriage. As mentioned previously, any patient with complaints that may be related to pregnancy (nausea, vomiting, abdominal pain, syncope, etc.) needs to have a pregnancy test in the ED. Similarly, any patient in the early stages of pregnancy with abdominal pain or vaginal bleeding should be evaluated for EP before the diagnosis of miscarriage can be made (Please see previous sections on EP).

When evaluating patients with suspected miscarriage, pertinent historical facts include dates and features of last menstrual period, drug use, obstetric and gynecologic history, as well as general medical and surgical histories. The physical exam should always include a pelvic exam, but this may be deferred to the obstetric consultant if the patient is nearing the end of the first half of pregnancy. In general, when the uterus is at the umbilicus by palpation, the patient is roughly 20 weeks pregnant. Vaginal exams are contraindicated in the second half of pregnancy when the patient presents with vaginal bleeding until placenta previa has been ruled out by ultrasound. Even minor trauma caused by a vaginal exam can result in catastrophic maternal hemorrhage in these patients.

In patients who are clearly in the early stages of pregnancy-(i.e., they have low beta-hCG levels and no significant uterine enlargement), the pelvic exam can be useful to verify that bleeding is coming from the os and not from a non-obstetrical cause such as hemorrhoids. Cultures for chlamydia and gonorrhea should be obtained. If there is bleeding from the os, one may determine if the os is open by gently attempting to pass a fingertip into the os, but one should never force the fingertip into the os. Probing with foreign objects (i.e., cotton swabs) is not recommended.

One should feel for adnexal masses or tenderness, and any tissue that is obtained should be sent for pathological verification of the presence of chorionic villi. Before sending the tissue to the lab, it can be examined in saline suspension using a low power microscope. Organized blood clots will appear firm with shredded edges, whereas chorionic villi appear with feathery edges. Up to 50% of specimens can be accurately identified by this means.[43] Diagnostic testing consists of quantitative beta-hCG and/or progesterone levels followed by transvaginal ultrasound (refer to previous discussion of diagnostic evaluation and diagnostic algorithms for EP).

The differential diagnosis of vaginal bleeding in the first half of pregnancy has been discussed. It is important to realize that spontaneous miscarriage is the most common misdiagnosis associated with EP. Several other disorders can easily be confused with spontaneous miscarriage. Hemorrhagic urinary tract infections (UTIs) can cause "vaginal bleeding" and can be differentiated using a catheterized urine specimen. An important point to remember is that all UTIs are treated in pregnancy to reduce the risk of miscarriage.

Non-obstetrical bleeding, such as hemorrhoids, also can occur. Cervical lesions are often friable and bleed easily. When a cervical lesion is found on exam, cervical carcinoma is always a concern. However, one should not biopsy these lesions in the ED as biopsy may lead to significant bleeding. Implantation bleeding is relatively common, and is more likely when it occurs around the time of an expected period. Bleeding can also be caused as the embryo invades the highly vascular endometrial tissue. The bleeding can vary from spotting to that associated with a normal period, and therefore, it can be a source of confusion for the patient when dates are calculated. Once EP has been ruled out, there are several types of spontaneous miscarriage that may be encountered. These are discussed in the sections below.

Threatened Miscarriage. A threatened miscarriage is defined as any amount of uterine bleeding in the first 20 weeks of pregnancy without passage of tissue or cervical dilation. The bleeding associated with threatened miscarriage can vary from a brownish discharge to bright red vaginal bleeding. The bleeding can start and stop repeatedly over the course of many days, and is often associated with uterine cramping or low backache.

On physical exam the cervix will be closed and uneffaced, and no tissue will be passed. Ultrasound can diagnose intrauterine pregnancy after as little as 5.5 weeks of gestation, but the ultrasound at 3-4 weeks gestation usually will be indeterminate.[44] Very early in pregnancy, an ultrasound finding of an empty uterus can still represent a normally developing pregnancy, an abnormal pregnancy destined to miscarry, or an ectopic. As mentioned above, ectopic must be ruled out using serial beta-hCG levels (or another diagnostic approach).

Ultrasonographic findings consistent with miscarriage include: abnormal gestational sac size or small embryo for dates, slow fetal heart rates, or large (> 20 mm) empty gestational sacs. In a recent ultrasound study of 78 women with intrauterine echogenic material (blood clots) with no gestational sac, all underwent spontaneous miscarriage.[45] Up to 95% of pregnancies will continue to live birth if a normal fetal heart rate is found at 8 weeks gestation.[46] The rate of pregnancy loss is only 1% when a live fetus is present at 14-16 weeks gestation.[44] To date there is no convincing evidence that any treatment will change the outcome in patients diagnosed with threatened miscarriage.

Patients with threatened abortion may be discharged with mandatory obstetrical follow-up and good return instructions (i.e., return for increased bleeding, passage of tissue, fever, worse pain, etc). Serial beta-hCG levels are typically followed as an outpatient and falling levels or decreasing gestational size on repeat ultrasound indicate a poor prognosis for the embryo. Alternatively, a single progesterone level may be predictive of fetal outcome. A single progesterone level over 25 ng/mL has been shown to be useful in predicting the presence of a viable pregnancy prognosis.[42,47] In a study of 358 women with threatened miscarriage, 148 had live births, 175 patients continued to spontaneous miscarriage, and there were 35 ectopic pregnancies. A single progesterone level over 25 ng/mL had a 90% sensitivity in discriminating between failing and non-failing pregnancies.[48]

Once fetal demise has occurred, the options for treatment include expectant management or uterine curettage. There has been debate in the literature as to whether expectant management or curettage is the better treatment. A pooled literature review found no difference between expectant management and surgical treatment; each was 93% successful.[49] Furthermore, expectant management has the advantage of a lower incidence of uterine perforation and infection compared to surgery. Another author found similar results, and suggested women with minimal intrauterine tissue, minimal bleeding or pain, and no signs of infection were good candidates for expectant management.[50] Medical management can be added in the form of prostaglandin (misoprostol) or antiprogesterone (mifepristone). However, a recent randomized trial found additional medical treatment was not superior to expectant management alone, and another author proposed larger trials to compare the two options.[51,52]

Inevitable/Incomplete Miscarriage. Although previously classified as separate entities, these two categorizations represent the same process of early pregnancy loss. They present in a similar fashion and are treated in a similar manner. Inevitable miscarriage is defined as vaginal bleeding or passage of tissue in conjunction with cervical dilation. An open cervix, defined as one through which a fingertip can easily pass into the os, is an important physical finding used to identify a spontaneous miscarriage.

Incomplete miscarriage occurs when products of conception have incompletely passed, a condition that usually is associated with vaginal bleeding and cramping. Retained tissue is more common in the second trimester and can result in profuse bleeding. Other than the occasional passage of only one twin, there is no fetal survival with inevitable or incomplete miscarriage. Complete evacuation of the uterus is advised to reduce maternal complications of bleeding and infection. Again, tissue obtained should be sent for pathological confirmation of villi to rule out the possibility of EP.

Uterine curettage can be performed as an outpatient, but the procedure should be executed by the consultant unless the ED physician is specifically trained in the procedure. Complications include blood loss, uterine perforation, and infection. After completion, the patient should be observed for several hours for signs of significant blood loss, and then followed-up with in 24-48 hours for re-examination and verification of falling beta-hCG levels.

Complete Miscarriage. A complete miscarriage occurs when all the products of conception have passed and vaginal bleeding has stopped. If the diagnosis is certain, no further treatment is required. If it is in question, ultrasound may be performed to evaluate for retained products. If these are detected, uterine curettage is the recommended treatment.

Missed Miscarriage. A missed miscarriage is defined by retention of products of conception for a prolonged period of time after documented fetal demise. The reason that some embryos do not spontaneously abort is unknown. Beta-hCG levels may fall to zero without passage of tissue, and the patient may no longer report symptoms of pregnancy. Most patients do eventually abort the fetus; coagulation defects from retained products of conception are rare in the first half of pregnancy. As expectant management may be emotionally difficult for the patient once diagnosed, most prefer uterine curettage for first trimester and dilation and curettage for second trimester cases.

Septic Miscarriage. Fortunately, the incidence of sepsis as a complication of miscarriage has dramatically decreased and is an uncommon cause of maternal mortality. Any type of spontaneous or elective miscarriage may lead to uterine infection and sepsis.

The patient will typically present with fever, abdominal pain/tenderness, and uterine pain. The patient may be unaware of the preceding pregnancy and miscarriage, or she may not be forthcoming with this history for multiple reasons.

The ED physician needs to maintain a high suspicion for this possibility when contemplating PID as an alternative diagnosis. In most cases, the beta-hCG will still be positive and should provide a clue to the diagnosis. In advanced cases, the patient may present in septic shock. When the diagnosis of uterine infection from miscarriage is considered, the patient needs to be treated for potential sepsis and receive fluid resuscitation.

Cervical cultures and gram stains, a tetanus booster when indicated, and flat/upright x-ray studies should be included to rule out free air or foreign bodies. The infections tend to be polymicrobial, and the following antibiotic regimens are recommended: Triple antibiotic coverage is used, with one choice from each category below. Coverage for gram-positive anaerobic or aerobic organisms can be provided with penicillin G, ampicillin, or any cephalosporin.[34] Gram-negative aerobic organisms are treated with aminoglycosides or aztreonam, and gram-negative anaerobic bacteria with clindamycin or metronidazole. Monotherapy with ampicillin/sulbactam, ticarcillin clavulanate, or piperacillin tazobactam is also acceptable.

Regardless of the choice, antibiotic coverage should be promptly administered. It is important to remember that early evacuation of the uterus is required for treatment of these patients and should be performed within several hours of presentation. Thus, prompt diagnosis and consultation are essential. Patients should be admitted to an ICU setting, as some will experience complications of sepsis syndrome (respiratory distress syndrome, coagulopathies, etc).

Rhesus Factor. When managing patients with EP or miscarriage, it can be easy to forget the Rh factor status. However, all pregnant patients with vaginal bleeding need a Rh factor test regardless of the cause. Almost 15% of patients are Rh negative and are at risk for carrying an Rh positive fetus. As Rh positive fathers greatly outnumber negative ones, and verification of the father's Rh status is problematic and impractical, any Rh negative mother is treated.

The maternal immune system will view the fetal blood as foreign and make antibodies against the Rh factor. As antibodies readily cross the placenta, any subsequent pregnancy will be at increased risk for hemolytic disease. This is often fatal for subsequent fetuses, so prevention is paramount. Sensitization can occur as early as eight weeks gestation, and the risk is estimated at 9% at 12 weeks gestation.[42] Recommendations are a 50 microgram IM injection of Rhogam (Rh immune globulin) for patients less than 12 weeks and 300 micrograms IM for patients greater than 12 weeks. As gestational dates can be notoriously inaccurate and there is no additional risk with the higher dose, many physicians opt for the 300 microgram dose in all patients. While Rhogam is ideally given at the time of ED presentation, it can be given up to 72 hours after bleeding and still be equally effective. Usefulness may be found even as late as 2-4 weeks after bleeding.[42]

Trophoblastic Disorders

Trophoblastic disorders represent abnormal proliferation of trophoblastic tissue. These disorders include complete mole (no recognizable fetal tissue), partial mole (fetal tissue with trophoblastic tissue), invasive hydatidiform mole, and choriocarcinoma.

Molar pregnancies can arise from a normal pregnancy, an EP, spontaneous miscarriage or an elective abortion. They occur in approximately 1 in 1000 pregnancies overall, with patients younger than 20 years or older than 40 years and women with a history of miscarriages being at increased risk.[53] The risk increases by at least fivefold in women who are older than 40 years of age. The risk increases tenfold if the patient has had a prior molar pregnancy. The risk of choriocarcinoma increases 5- to 24-fold for women older than 40 years of age. However, the most important risk factor of choriocarcinoma is a history of a hydatidiform mole. The risk of choriocarcinoma in these patients has been estimated to be 1000 times that of the general population.[54]

Patients with trophoblastic disorder most commonly present with vaginal bleeding, severe or persistent hyperemesis, and early development of preeclampsia. As the trophoblastic tissue expands at a much faster rate than a normal pregnancy, a large uterus for dates is often found on exam. Quantitative beta-hCG levels are also much higher than those found in normal pregnancy. Ultrasound will show a "snow storm" pattern secondary to the molar vesicles.[4] Fifteen percent of molar pregnancies can progress to choriocarcinoma, which can metastasize to the lungs, vagina, brain, liver, bowel, spleen, or kidney.[52]

A patient who presents to the ED and is found to have trophoblastic disease should have a chest x-ray to rule out pulmonary metastases. Obstetric consultation is mandatory in all cases. Depending on the age of the patient and the desire for fertility, treatment consists of dilation and curettage or hysterectomy. A beta-hCG level should be obtained each week following treatment until levels have normalized for three weeks. Levels should then be drawn monthly for 6-12 months. The patient should use contraception for at least one year following the molar pregnancy.[52] Chemotherapy is utilized in choriocarcinoma and in molar pregnancies that have stable or rising beta-hCG levels. Fortunately, trophoblastic disease is highly responsive to chemotherapy.

Summary

The diagnosis of pregnancy can be easily overlooked in the ED. Bleeding complications during the first half of pregnancy are common, and any patient with vaginal bleeding, abdominal pain, or other symptoms of pregnancy should have pregnancy ruled out. If the patient is found to be pregnant, EP should be ruled out. EP is still a leading cause of maternal death. The ED physician needs to maintain a high index of suspicion for these patients to reduce potential morbidity and mortality. Patients should also be evaluated for spontaneous miscarriage or its complications, as well as trophoblastic disease. Rhogam should be given to all Rh-negative patients.

Obstetrical consultation will be required for most patients

while in the ED, and certainly all will require further follow up visits with an obstetrician. Finally, as the grief reaction of early pregnancy loss can be severe in some patients, referral to psychiatric counseling or social worker consultation before discharge should be considered. These reactions are common in the ED, as a recent study of 44 ED patients with spontaneous miscarriage found that 80% experienced a significant grief reaction.[55]

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Physician CME Questions

1. The incidence of molar pregnancies is approximately:
   A. 1 in 10 pregnancies overall.
   B. 1 in 100 pregnancies overall.
   C. 1 in 1000 pregnancies overall.
   D. 1 in 10,000 pregnancies overall.

2. The beta-hCG discriminatory threshold for EP is approximately:
   A. 15 mIU/mL.
   B. 150 mIU/mL.
   C. 1500 mIU/mL.
   D. 15,000 mIU/mL.

3. Approximately what percentage of patients with EP will have signs of hemodynamic instability or significant peritonitis?
   A. 5%
   B. 20%
   C. 40%
   D. 50%

4. Contraindications to medical management (methotrexate) of EP include which of the following?
   A. Rupture
   B. Diameter of adnexal mass > 3-4 cm on ultrasound
   C. Evidence of fetal cardiac activity
   D. Beta-hCG > than 2000 mIU/mL
   E. All of the above

5. Approximately what percentage of women will experience vaginal bleeding during the first 20 weeks of pregnancy, and up to what percentage of these will have a miscarriage?
   A. 10% will bleed, up to 20% of these will miscarry.
   B. 10% will bleed, up to 30% of these will miscarry.
   C. 20% will bleed, up to 50% of these will miscarry.
   D. 50% will bleed, up to 75% of these will miscarry.

6. Ultrasonographic findings consistent with miscarriage include which of the following?
   A. Abnormal gestational size sac
   B. Small embryo for date
   C. Slow fetal heart rate
   D. Large (> 20 mm) empty gestational sac
   E. All of the above

7. A single progesterone level over 25 ng/mL had a 90% sensitiivty in discriminating between failing and non-failing pregnancies.
   A. True
   B. False

8. The rate of pregnancy loss in women who have a live fetus present at 14-16 weeks of gestation is about:
   A. 1%.
   B. 10%.
   C. 20%.
   D. 30%.

In Future Issues:

Bleeding in the Second 20 Weeks of Pregnancy